19/Appeal Brief (3)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Gerald Wynn HALLWORTH

Serial No.: 09/651,083

Filed: August 30, 2000

For: INHALATION COMPOSITION CONTAINING LACTOSE PELLETS

Group Art Unit: 1615

Examiner: A. Pulliam

Bet 2-9-03

BRIEF ON APPEAL

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This brief on appeal is submitted in triplicate. The required appeal fee for submission with the brief is enclosed. The Commissioner is hereby authorized to charge any further fee necessary to this appeal to Deposit Account No. 02-0200.

I. REAL PARTY IN INTEREST

The real party in interest is the Assignee of record, Glaxo Group Limited.

II. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences with respect to the claimed invention which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal known to appellant, appellant's legal representative or assignee.

III. STATUS OF THE CLAIMS

This application contains 1 through 39. Claims 1-17, 20, 34 and 35 have been canceled from the application.

Claims 18, 19, 21-33 and 36 through 39 are pending and are the claims on appeal. Claims 18, 19, 21-33 and 36 through 39 stand finally rejected.

IV. STATUS OF AMENDMENTS AFTER FINAL REJECTION

No amendment was filed after final rejection.

V. SUMMARY OF INVENTION

The present invention relates to an improved pharmaceutical powder composition suitable for inhalation. (Page 1, lines 1 and 2.)

Numerous medicaments, especially those for the treatment of respiratory conditions such as asthma, are administered by inhalation. Since the drug acts directly on the target organ much smaller quantities of the active ingredient may be used, thereby minimising any potential side effects caused as a result of systemic absorption. The efficacy of this route of administration has been limited by the problems encountered in making appropriate and consistent dosages available to the lungs. The delivery systems currently available are pressurized metered dose inhalers, nebulizers and dry powder inhalers. (Page 1, lines 4 to 11.)

It has been found that medicaments for administration by inhalation should be of a controlled particle size in order to achieve maximum penetration into the lungs, preferably in the range of 1 to 10 micrometres in diameter. Unfortunately, powders in this particle size range, for example micronised powders, have a high bulk volume and have very poor flow characteristics due to the cohesive forces between the individual

particles. These characteristics create handling and metering difficulties during manufacture of the medicament powder and, most importantly, adversely affect the accurate dispensing of the powder within the inhalation device. (Page 1, lines 20 to 28).

According to the present invention there is provided a pharmaceutical powder composition suitable for inhalation which comprises microfine particles of medicament and at least one lactose pellet having a diameter of from about 10 to about 1500 micrometres, which pellet comprises a plurality of microfine lactose particles. (Page 2, lines 15 to 19.)

The particle size of the "microfine" particles of medicament and lactose should be such as to permit substantially all of the particles to be potentially available for inhalation into the lungs upon administration of the powder composition. Thus, for example, at least 90%, preferably at least 95% by weight of the particles will have a diameter of less than 15 micrometres. (Page 2, line 20 to 25.)

Medicaments which may be administered in the powder compositions according to the invention include any drugs usefully delivered by inhalation. (Page 2, lines 26 to 27.)

Particularly preferred medicaments for administration using powder compositions in accordance with the invention include anti-allergics, bronchodilators and anti-inflammatory steroids of use in the treatment of respiratory disorders such as asthma by inhalation therapy. (Page 3, lines 14 to 17.)

It will be appreciated by those skilled in the art that the powder compositions according to the invention may, if desired, contain a combination of two or more active ingredients. (Page 3, lines 26 to 28.)

The internal strength or coherence of the lactose pellets of use in the present invention may be high ("hard" lactose pellets) or low ("soft" lactose pellets) or a mixture of "hard" and "soft" pellets. However, a preferred embodiment of the invention contains "soft" lactose pellets with a low internal coherence. These lactose pellets are friable and have an internal coherence such that the pellets remain substantially intact under conditions of packaging, transport, storage and when fluidised within a container in the inhalation device from which it is intended to dispense the composition according to the

invention e.g. unit dose container or bulk reservoir and yet may be disrupted into independent microfine lactose particles upon egress into the turbulent air stream within the mouthpiece of the inhaler device. (Page 4, lines 10 to 20.)

VI. ISSUES

The issues on appeal are whether claim 18 is anticipated by the Hartley et al. reference under 35 USC 102(b) and whether claims 18, 19, 21-33 and 36 through 39 are prima facie obvious over the Hartley et al reference.

VII. GROUPING OF THE CLAIMS

The claims as grouped in the Final Rejection do not stand or fall together.

VIII. ARGUMENT

THE ANTICIPATION ISSUE

The Final Rejection states that Hartley et al teaches that according to a specific feature of their invention, sodium cromoglycate, having an effective particle size of from 0.01 to 10 microns, is useful for mixing with lactose of particle size from 30 to 80 microns in order to produce a composition suitable for inhalation. The Final Rejection refers to column 3, lines 56-65 of the Hartley et al reference.

Appellant has also considered the comments in the Final Rejection with respect to the Hartley et al reference, especially at column 1, lines 51-56 which points out that for the purposes of the Hartley et al. invention there is no distinction between a single particle of given size and an agglomerate of the same size which is composed of finer individual particles. The term "effective particle size" is therefore used in Hartley et al.

to denote the apparent particle size of the body without distinction as to the number of individual particles which go to make up that body.

MPEP § 2131 states that to anticipate a claim, the reference must teach every element of the claim.

> "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed Cir. 1989). The elements must be arranged as required by the claim, but this is not an *ipsissimis verbis* test, i.e., identity of terminology is not required. *In re Bond*, 910 F.2d 831, 15 USPQ2d 1566 (Fed.Cir. 1990). Emphasis added.

Appellant notes that claim 18 requires a pharmaceutical powder composition suitable for inhalation comprising microfine particles of medicament and at least one preformed lactose pellet having a diameter of from about 10 to about 1500 micrometers, which pellet comprises a plurality of microfine lactose particles, wherein at least about 90% by weight of the microfine particles of lactose have a diameter of less than about 15 micrometers. These claim limitations must be shown in the same detail in the reference as in claim 18. The Examiner has not pointed to any portion of the reference which show these claim limitations. The reference does not anticipate claim 18.

At column 2 of the patent, line 50, it is noted that a particularly preferred diluent or carrier is crystalline lactose. The specification contains two specific examples, examples 1 and 2, as set forth beginning at the bottom of column 3 of the patent. Example 1 describes the use of commercially available ground crystalline lactose having an effective particle size of from 0.01 to 100 microns (less than 30 percent by weight greater than 60 microns, not more than 30 percent by weight less than 30 microns) which was passed through an air classifier, set to remove material having an effective particle size of less than 30 microns.

The patent does not state whether the ground crystalline lactose used in the examples are a single particle or an agglomeration of finer particles. However, it is noted that the lactose particles have been subjected to grinding. The friable lactose pellets of the present invention are designed to break up on delivery to the inhaling patient and it would be fully appreciated by one of ordinary skill in the art that such friable pellets could not withstand a grinding process. Clearly, one of ordinary skill in the art would appreciate that the lactose particles of Hartley et al were not present in the form of a pellet in accordance with the present invention. Accordingly, there is no anticipation.

In this regard, the Examiner's attention is most respectfully directed to page 4 of Appellant's specification which discusses the internal strength or coherence of the lactose pellets for use in the present invention. These may be either hard or soft lactose pellets or a mixture of hard and soft pellets. It is noted that in a preferred embodiment the lactose pellets are soft and contain a low internal coherence. These lactose pellets are friable and have an internal coherence such that the pellets remain substantially intact under conditions of packing, transport, storage and when fluidised within a container in the inhalation device from which it is intended to be disposed, the composition according to the invention, e.g., unit dose container or bulk reservoir may be disrupted into independent microfine lactose particles upon egress into the turbulent airstream within the mouthpiece of the inhaler device. Clearly, the lactose pellet of claim 18 is not anticipated by the teachings of Hartley et al as would be fairly interpreted by one of ordinary skill in the art to which the invention pertains. There clearly is no explicit teaching of the claim limitations with respect to the particle size of the particles making the claimed pellet in Hartley et al reference and one of ordinary skill in the art would appreciate that the examples do not inherently contain such a pellet in view of the grinding processing steps in the example.

To serve as an anticipation when the reference is silent about the asserted inherent characteristic, the size characteristics of the microfine particles of claim 18 in this case, this silence in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily

present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. In re Oelrich, 666 F.2d 578, 581,212 USPQ 323, 326 (CCPA 1981) (quoting Hansgirg v. Kemmer, 102 F.2d 212, 214, 40 USPQ 665, 667 (CCPA 1939)) provides:

> Inherency, however may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient. [Citations omitted.] If, however, the disclosure is sufficient to show that the natural result flowing from the operation as taught would result in the performance of the questioned function, it seems to be well settled that the disclosure should be regarded as sufficient. This modest flexibility in the rule that "anticipation" requires that every element of the claims appear in a single reference accommodates situations where the common knowledge of technologists is not recorded in the reference....l

However, the Examiner supplies no extrinsic evidence or sound reasoning based on the reference to establish that the claim limitations are present in the reference agglomerates. No other references are applied in the rejection. The Examiner relies upon the teaching of the reference at column 1, lines 52-60, where it states that there is no distinction between a single particle of a given size and an agglomerate of the same size composed of finer individual particles. While this may be true with respect to the Hartley et al invention, it is certainly not true with respect to the presently claimed invention. This teaching neither explicitly nor inherently teaches the limitation of claim 18 for the fine lactose particles which are an important part of the claimed invention. As explained in Appellants' specification," The particle size of the "microfine" particles of medicament **and lactose** should be such as **to permit substantially all of the particles** to be potentially available for inhalation into the lungs upon administration of the powder composition". Thus, for example, at least 90%, preferably at least 95% by weight of the particles will have a diameter of less than 15 micrometres. As clearly set forth in Hartley et al, particles need to be in the 0.01-10 micron range for maximum penetration into the lungs. Hartley et al is not concerned about the particle size of the

lactose particles for entry into the lungs in accordance with the present invention but only the flow characteristics of the particles described therein.

As would be appreciated by one of ordinary skill in the art, the equivalency cited by the Examiner in Hartley et al is for the flow characteristics and does not inherently suggest the friability and the fine particle size of the pellet of the present invention.

In addition, the Examiner points to column 4, lines 46-55, where Hartley *et al.* state, "by way of comparison composition[s] containing no coarse diluent was prepared and tested in each case. Those compositions containing the coarse carrier were all found to empty from the capsule at a satisfactory rate, in general from 85 to 90 percent of the composition, whereas in the absence of the coarse diluent the emptying rates were much lower, about 15 percent or less, and were unpredictable." This in no way either explicitly or implicitly teaches the claim limitation of claim 18 for the microfine lactose particles for entry into the lungs after removal from a gelatin capsule. There is no disclosure in Hartley of the further break down (friability) of the lactose required by the present invention.

Additionally, Hartley *et al.* is said to discuss that the particular compositions which were compared are discussed in table 1 and that Hartley *et al.* would not have provided information comparing compositions with and without coarse diluent, if all of their compositions ground the lactose to fine particles. However, Appellant does not agree with the Examiner's position that Hartley *et al.* teach larger lactose particles made of agglomerated smaller finer particles. The Hartley et al tables only show the advantage of having lactose particles of a size of 30 to 80 microns present with the medicament to facilitate the flow of the medicament of 0.01 to 10 microns size from the gelatin capsule. It does not say anything about the microfine lactose particles which form the lactose pellets of the present invention which are friable and form the microfine lactose particles for inhalation. Accordingly, it is most respectfully requested that the rejection under 35 U.S.C. 102(b) be reversed.

THE OBVIOUSNESS ISSUE

Basic Requirements of a Prima Facies Case of Obviousness

The appellant believes that the criteria set forth in the MPEP provides guidance in determining the issue of obviousness of the claims on appeal over the prior art of record.

MPEP § 2143 Basic Requirements of a Prima Facie Case of Obviousness

To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

MPEP §2143.03 All Claim Limitations Must Be Taught or Suggested

To establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." In re Wilson, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). If an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious. In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

In the obviousness rejection, the Examiner urges that for the reasons discussed in the anticipation rejection, Hartley et al teaches a composition suitable for inhalation

comprising sodium cromoglycate and lactose particles. However, Appellant submits that for the reasons discussed above there is no teaching of the composition of the present invention containing a friable lactose pellet of claim 18 on appeal.

That is, Hartley et al neither explicitly nor inherently teaches the limitation of claim 18 for the fine lactose particles which form the pellet and which is an important part of the invention. As explained in Appellants' specification," The particle size of the "microfine" particles of medicament **and lactose** should be such as **to permit substantially all of the particles** to be potentially available for inhalation into the lungs upon administration of the powder composition". Thus, for example, at least 90%, preferably at least 95% by weight of the particles will have a diameter of less than 15 micrometres. Hartley et al does not recognized this aspect of the invention.

As clearly set forth in Hartley et al, the medicament particles need to be in the 0.01-10 micron range for maximum penetration into the lungs. There is no recognition in Hartley et al that the lactose particles should be in this size range. The teaching is for a lactose particle size range of 30 to 80 microns and that it does not matter if the lactose of this size is a single particle or an agglomerate of fine particles. Hartley et al is not concerned with the particle size of the lactose particles for entry into the lungs in accordance with the present invention but only with the flow characteristics of the composition containing lactose particles, another aspect of the present invention. Clearly, from Hartley et al's own teaching that the effective particle size of the lactose carrier is from 30 to 80 microns and the equivalence of a single particle or agglomerate, there is no teaching of the friable lactose pellet form of microfine particles of lactose of the claims on appeal. For Appellants' invention, it is a critical limitation that the friable lactose pellet is composed of particles of a size of less than about 15 microns. There is no motivation in Hartley et al to make the necessary modifications to arrive at the presently claimed invention. In re Fritch, 23 USPQ 1780, 1784(Fed Cir. 1992) ("It is impermissible to engage in hindsight reconstruction of the claimed invention, using the applicant's structure as a template and selecting elements from references to fill the gaps.).

Additionally, it is urged in the Final Rejection that the burden is shifted to applicant to show a finding of unexpected results using specific sizes of lactose particles and that currently, it appears that the teachings of Hartley *et al.* fulfill the same purpose as applicant's claimed invention. The same purpose is not achieved since the pellets of the present invention are friable and particles of lactose having a diameter of less than about 15 micrometers are available for penetration into the lungs. It is most respectfully submitted that the Examiner has the burden of presenting a prima facie case of obviousness which has not been done.

Hartley *et al.* also do not teach each of the specific drugs claimed by applicant. However, Hartley *et al.* do teach that their compositions may contain any of a wide variety of medicaments suitable for administration of inhalation (column 2, lines 13-15). It is the position of the examiner that one of ordinary skill in the art would have been motivated to use any drug, which is known for use in inhalation therapy, in the composition disclosed by Hartley *et al.*, which is taught to be successful for inhalation use. The expected result would be a successful composition for inhalation therapy. However, the substitution of an additional known drug does not overcome the deficiencies with respect to the claim limitations for the lactose pellet of the independent claim and this claim is equally allowable.

The limitations of claims 22, 23, 38 and 39 are also clearly not suggested by Hartley et al. Claims 22 and 23 relate to a pharmaceutical powder composition which contains a soft lactose pellet having a crushing weight of about 50 to 500 mg and claim 23 is limited to a crushing weight of about 50 to 100 mg. Claims 38 and 39 further define pellet size. There is absolutely no suggestion in the Hartley et al reference which would lead one of ordinary skill in the art to a pellet having these limitations, especially in view of the teaching of equivalence between a single particle and an agglomerate. There is no recognition of the advantage of having a friable lactose pellet of microfine particles for entry into the lungs after crushing in the administering device, i.e., inhaler.

As previously noted, this crushing weight is described on page 4, second full paragraph of Appellant's specification. It is noted that the soft lactose pellets with a low internal coherence represent a preferred aspect of the invention. As noted, these

lactose pellets are friable and have an internal coherence such that the pellets remain substantially intact under conditions of packaging, transport, storage and when fluidised within a container in the inhalation device for which it is intended to dispense the composition according to the invention, i.e., unit dose container a bulk reservoir and yet may be distributed into independent microfine lactose particles upon egress in the turbulent airstream within the mouthpiece of the inhaler device. There is no recognition of this advantage in Hartley et al reference including no motivation to arrive at the claimed subject matter with these characteristics. Obvious to try is not the standard of obviousness under 35 USC 103.

Appellant has clearly established that the claimed products are functionally different in mode of delivery of microfine lactose particles to the lungs and the burden is on the Examiner to establish a prima facie case of obviousness. Accordingly, this aspect of the rejection should be reversed.

Appellant also most respectfully submits that the processes set forth in claims 29 and 30 are not suggested by the prior art. Again, there is no discussion of the formation of a pellet from microfine particles of lactose of with 90% having a particle size of less than 15 microns. The lactose pellets of the present invention are friable and the process coating the lactose pellets with a liquid suspension or solution of medicament is not suggested by the Hartley et al reference. There is no discussion in the reference which would suggest the limitations of these claims from the prior art and Applicants' specification may not be used as a teaching reference and this aspect of the rejection is clearly based upon hindsight. Accordingly, it is most respectfully requested that this aspect of the rejection be reversed.

ADDITIONAL CUMULATIVE PRIOR ART

Appellants submit herewith additional cumulative prior art. It is requested that this prior art be place in the file.

IX. CONCLUSION

In view of the above arguments, the rejections of the claims on appeal should not be sustained. The Final Rejection should be reversed and the application passed to issue.

Respectfully submitted,

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APPENDIX

CLAIMS ON APPEAL

18. A pharmaceutical powder composition suitable for inhalation comprising microfine particles of medicament and at least one preformed lactose pellet having a diameter of from about 10 to about 1500 micrometers, which pellet comprises a plurality of microfine lactose particles, wherein at least about 90% by weight of the microfine particles of lactose have a diameter of less than about 15 micrometers, and wherein the medicament is selected from the group consisting of codeine, dihydromorphine, ergotamine, fentanyl, morphine, diltiazem, cromoglycate, ketotifen, nedocromil, cephalosporins, penicillins, streptomycin, sulphonamides, tetracyclines, pentamidine, methapyrilene, budenoside, flunisolide, tipredane, triamcinolone acetonide, noscapine, ephedrine, adrenaline, fenoterol, formoterol, isoprenaline, metaproterenol, phenylephrine, phenylpropenolamine, pirbuterol, reproterol, rimeterol, terbutaline, isoetharine, tulobuterol, orciprenaline, (-)-4-amino-3,5-dichloro-a-[[[6-[-2-(2-pyridinyl)ethoxy]hexyl]-amino]methyl]benzenemethanol, amiloride, ipratropium, atropine, oxitropium, cortisone, hydrocortisone, prednisolone, aminophylline, choline theophyllinate, lysine theophyllinate, theophylline, insulin, glucagon and any mixtures thereof.

19. A pharmaceutical powder composition according to claim 18, wherein said at least one lactose pellet has a diameter of from about 150 to 1000 micrometers.

21. A pharmaceutical powder composition according to claim 18, wherein said at least one lactose pellet is hard or soft.

22. A pharmaceutical powder composition according to claim 21, wherein the soft lactose pellet has a crushing weight of about 50 to about 500 mg.

23. A pharmaceutical powder composition according to claim 22, wherein the soft lactose pellet has a crushing weight of about 50 to about 100 mg.

24. A pharmaceutical powder composition according to claim 18, wherein the medicament is ~~turbutaline sulphate~~.

25. A pharmaceutical powder composition according to claim 18, wherein the medicament is formoterol.

26. A pharmaceutical powder composition according to claim 18, wherein the medicament is budenoside.

27. A pharmaceutical powder composition according to claim 18, wherein the medicament comprises a mixture of formoterol and budenoside.

28. A pharmaceutical composition according to claim 18, wherein the microfine particles of medicament form at least one medicament pellet.

29. A process for preparing a pharmaceutical composition according to claim 18, comprising admixing microfine particles of medicament with at least one lactose pellet having a diameter of from about 10 to about 1500 micrometers, which pellet comprises a plurality of microfine lactose particles.

30. A process according to claim 29, wherein the admixing comprises coating the lactose pellets with a liquid suspension or solution of medicament.

31. An inhalation device comprising a ~~compound~~ according to claim 18.

32. A composition according to claim 18, wherein the medicament is selected from the group consisting of anti-allergics, bronchodilators, anti-inflammatory steroids and mixtures thereof, for use in the treatment of respiratory disorders.

33. A method of treating respiratory disorders which comprises administration by inhalation of an effective amount of a pharmaceutical powder composition ~~which~~ comprises microfine particles of medicament selected from the group consisting of anti-allergics, bronchodilators, anti-inflammatory steroids and mixtures thereof and at least one lactose pellet having a diameter of from about 10 to about 1500 micrometers, which pellet comprises a plurality of microfine lactose particles, and wherein at least about 90% by weight of the microfine particles of lactose have a diameter of less than about ~~15 micrometers~~.

36. A pharmaceutical powder composition according to claim 22, wherein the medicament is selected from the group consisting of salmeterol xinafoate, salbutamol sulphate and fluticasone propionate.

37. A pharmaceutical powder composition according to claim 23, wherein the medicament is selected from the group consisting of salmeterol xinafoate, salbutamol sulphate and fluticasone propionate.

38. A pharmaceutical powder composition according to claim 18, wherein said at least one lactose pellet has a diameter form about 150 to 1000 micrometers and wherein at least about 90% by way of the microfine particles of lactose have a diameter of less than about 15 micrometers and wherein the lactose pellet is a soft lactose pellet having a crushing weight of about 50 to about 150 mg.

39. A pharmaceutical powder composition according to claim 38, wherein the soft lactose pellet has a crushing weight of about 50 to about 100 mg.